REMARKS

Claims 1-8 are pending in the application and have been examined. Claims 1-8 stand rejected. Claims 1, 2, 4, 5, and 6 have been amended. Claims 3 and 7-42 have been canceled. Claims 43-46 have been added. No new matter has been introduced. Reconsideration and allowance of Claims 1, 2, 4-6, and 43-46 is respectfully requested.

The Objection to the Specification

The specification has been amended to capitalize the trademarks GENBANK, AMPLICYCLE, BIGDYE, and SEQUENCHER, as requested by the Examiner. No new matter has been introduced.

The Rejection of Claims 1-8 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-8 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner has taken the position that the specification fails to provide enough guidance for one skilled in the art on how to practice the full scope of the instant method, thereby requiring undue experimentation to discover how to use applicants' invention. Applicants disagree for the following reasons.

As an initial matter, it is noted that Claims 1, 2, 4, 5, and 6 have been amended to clarify the claimed invention. Claims 3, 7, and 8 have been canceled. Claim 1, from which Claims 2, 4, 5, and 6 depend, recites as amended:

> Claim 1. (Currently amended) A method of identifying genetic mutations that are associated with ataxic neurological disease in a human subject, said method comprising:
>
> (a) determining a first nucleic acid sequence of a human protein kinase C gamma gene from a first human subject exhibiting ataxia;
>
> (b) identifying a difference between the first nucleic acid sequence from the first human subject exhibiting ataxia and SEQ ID NO:3; and

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(c) confirming that the difference identified between the first nucleic acid sequence and SEQ ID NO:3 is a genetic mutation associated with ataxia by co-segregation analysis comprising determining that the identified nucleic acid sequence difference is also present in a plurality of human subjects exhibiting ataxia and is absent in a plurality of human subjects not exhibiting ataxia.

Support for the amendment is found throughout the specification as filed, *e.g.*, at page 6, lines 23-32; page 11, line 11, to page 13, line 24; and page 23, line 16, to page 30, line 14.

1. The Examiner has failed to establish a prima facie case of non-enablement

As an initial matter, it is submitted that the Examiner has not met the required burden of establishing a reasonable basis to question the enablement provided in the specification for the claimed invention.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C.§ 112, first paragraph, unless there is a reasons to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

M.P.E.P. 2164.04 citing *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q.367,369 (C.C.P.A. 1971) (emphasis in the original). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is consistent with the contested statement." *Id.* at 224, 169 U.S.P.Q. at 370.

It is submitted that Claims 1, 2, 4, 5, and 6 are enabled by the specification as filed in view of the knowledge of the skilled artisan at the time the application was filed. The Examiner has taken the view that the claims are drawn to methods in which any mutation in the protein kinase C gamma gene of any mammal exhibiting ataxia is considered to be associated with ataxic neurological disease. In this regard, it is noted that Claim 1, as amended, specifies the identification of a difference between a first nucleic acid sequence of a human protein kinase C gamma gene from a first *human* subject exhibiting ataxia and *SEQ ID NO:3*, and confirming that

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the difference identified is a genetic mutation associated with ataxia by co-segregation analysis in *human* subjects.

2. *Adequate guidance is provided in the specification for one of skill in the art to practice the claimed method without undue experimentation*

The Examiner has taken the view that the specification does not provide adequate guidance for one skilled in the art on how to practice the full scope of the instant method without undue experimentation. In this regard, it is noted that the Examiner acknowledges that the specification discloses:

> . . . a particular mutation, the 'C to T transition in nucleotide 301 (H101Y),' that was identified by screening the protein kinase C gamma gene in healthy and diseased populations of human subjects, and which is clearly associated with a particular type of ataxia (the 'unexplained cerebellar ataxia' discussed in Example 1) in a particular type of subject (humans), such that one of skill in the art could clearly practice methods of e.g., diagnosing predisposition to this type of ataxia in a human subject by detecting the presence of this particular alteration in the protein kinase C gamma gene of the human subject.

(See page 5 of Non-Final Office Action mailed February 15, 2007.) The Examiner further acknowledges:

> [g]iven the high level of skill of one skilled in the art relevant to the claimed invention, it is clearly within the ability of such an artisan to conduct screening methods, e.g., employing samples from other types of mammals and/or patients with other types of ataxia so as to determine whether other mutations associated with ataxia exist in the protein kinase C gene of such subjects.

(See page 6 of Non-Final Office Action mailed February 15, 2007.) However, the Examiner concludes that the outcome of such experimentation cannot be predicted. Applicants respectfully disagree.

It is submitted that the claimed invention is enabled by the specification as filed in view of the knowledge of one skilled in the art at the time of filing. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in a patent

coupled with information known in the art without undue experimentation. With respect to what constitutes undue experimentation, the following factors are relevant: the breadth of the claims; the nature of the invention; the state of the prior art, the relative skill of those in the art; the predictability of the art; the amount of guidance provided; the presence of working examples; and the quantity of experimentation necessary. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (stating "the key word is undue, not experimentation."). As further pointed out by the Federal Circuit, ". . . the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of enablement must not be unduly extensive." *PPG Indus., Ind. v. Guardian Indus., Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The specification provides a detailed description of methods of identifying genetic mutations that are associated with ataxia in a human subject, as well as working examples describing the successful identification of several such genetic mutations. For example, as described in the specification, any method of obtaining reliable nucleic acid sequence data from a mammalian subject, such as a human exhibiting ataxia, may be utilized. (See specification at page 7, line 1, to page 8, line 12.) Numerous methods are described for DNA sequencing and co-segregation analysis, all of which are well known and routine in the art at the time of filing. (See specification at page 8, line 13, to page 13, line 24.) The full sequence of SEQ ID NO:3 is provided in the specification along with exemplary primers, provided in TABLE 1 and TABLE 2, for PCR amplification and sequencing SEQ ID NO:3 from genomic DNA. Moreover, working examples are provided that describe the identification of several mutations that are associated with ataxia in human subjects (*e.g.* H101Y in Example 1, S119P and G128D in Example 2 and R41P, S361G and R597S in Example 3) in accordance with the methods of the claimed invention.

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It is further submitted that adequate guidance is provided in the specification to enable one skilled in the art to determine whether a genetic mutation in SEQ ID NO:3 co-segregates with ataxia. As described in the specification:

> . . . the term 'genetic mutation' is an alteration of the wild-type protein kinase C gamma (PRKCG) sequence deposited in GENBANK, provided as SEQ ID NO:3 that is not a recognized polymorphism (i.e., has a population frequency less than 1% in mammalian control subjects of the same species that do not exhibit ataxia).

(See specification at page 5, lines 1-4.) As further described in the specification:

> . . . once a mutation is identified in a subject exhibiting ataxia, co-segregation analysis is carried out to determine if the particular mutation in the PRKCG co-segregates with the presence of ataxic neurological disease symptoms in the subjects tested.

(Specification at page 11, line 30, to page 12, line 1.) The specification provides examples of various methods that can be used to perform co-segregation analysis including, but not limited to, single stranded conformation analysis (SSCA), denaturing gradient gel electrophoresis (DGGE), RNAse protection assays, hybridization with allele-specific oligonucleotides, allele-specific PCR, and restriction fragment length polymorphism (RFLP). (See specification at page 12, line 1, to page 13, line 24.)

Moreover, the specification also provides working examples of co-segregation analysis. For example, as described in Example 1, a study was done in which the presence of the H101Y mutation was found in ten subjects exhibiting ataxia and was not found in 192 normal control subjects. (See specification at page 25, lines 4-10.) As described in Example 2, the S119P mutation was found in three human subjects exhibiting ataxia, and was not found in 96 control subjects. (See specification at page 26, lines 5-17.)

Therefore, it is submitted that the specification provides adequate guidance for one of skill in the art to practice the method of the invention as claimed.

3. It Would Not Require Undue Experimentation to Practice the Claimed Invention

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The Examiner has taken the view that it is unpredictable as to whether one of skill in the art could practice the invention of the instant claims.

Contrary to the Examiner's assertion, it is submitted that the routine nature of the screening for mutations that are associated with ataxia is entirely consistent with the holding in *Wands*. As stated in *Wands*, "[e]nablement is not precluded by some experimentation, such as *routine screening*." *Wands*, 858 F.2d at 736-37 (emphasis added). As further stated in *Wands*:

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Wands, 858 F.2d at 736-737.

As further evidence of the routine nature of the experimentation required to practice the claimed invention, in view of the guidance provided in the instant specification, applicants wish to point out that additional mutations in the protein kinase C gamma gene (SEQ ID NO:3) that co-segregate with ataxia have successfully been identified by others in the field. For example, Nolte, D. et al., *Movement Disorders 22*(2): 265-267 (2007), attached hereto as Attachment A, describes the identification of the mutation G63V in two human subjects exhibiting ataxia which was not detected in control chromosomes from 200 healthy control subjects. In addition, as summarized in TABLE 1 of Nolte et al., numerous other mutations that co-segregate with ataxia have been identified by others in the field.

Therefore, applying the *Wands* factors to the instant application, it is apparent that a reasonable correlation exists between the scope asserted in the claimed subject matter and the scope of guidance provided by the specification in view of the knowledge of those skilled in the art. Applicants respectfully request removal of this ground of rejection.

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The Rejection of Claims 1-8 Under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)

Claims 1-8 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to distinctly claim the subject matter which applicants regard as the invention.

Claims 1, 2, 4, 5, and 6 have been amended to clarify the claimed invention. Claims 3, 7 and 8 have been canceled.

Claim 1 has been amended as described above to clarify the claimed invention. The rejection of Claims 4-6 for insufficient antecedent basis is moot in view of the amendment to Claim 1 described above. Finally, Claim 6 has been amended to remove the language "aberrant restriction enzyme site."

Removal of this ground of rejection is respectfully requested.

New Claims 43-46

Claims 43-46 have been added which depend either directly or indirectly from Claim 1. Claims 43 and 44 specify particular portions of SEQ ID NO:3 that are amplified for sequencing. Support for this subject matter is found throughout the specification as filed, for example, at page 6, lines 6-22.

Claims 45 and 46 have been added which depend either directly or indirectly from Claim 1 and specify various types of genetic mutations associated with ataxia. Support for this subject matter is found throughout the specification as filed, for example, at page 11, lines 11-29.

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CONCLUSION

In view of the foregoing, applicants submit that all of the pending claims are in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

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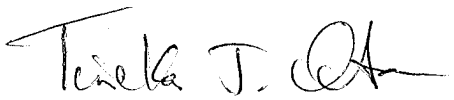

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Attachment A

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ATTACHMENT A

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Spinocerebellar Ataxia 14: Novel Mutation in Exon 2 of *PRKCG* in a German Family

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Abstract: **We describe a novel mutation in the gene coding for protein kinase C gamma (*PRKCG*) in patients of a German family affected with slowly progressive gait ataxia, dysarthria, and nystagmus. The G/T missense mutation occurred in exon 2 of *PRKCG* and results in a substitution of glycine by valine (G63V) in the evolutionarily highly conserved cysteine-rich region 1/C1 domain of PRKCG. Among the 20 mutations described to date, this is the first mutation located in exon 2 of *PRKCG*.** © 2006 Movement Disorder Society

Key words: spinocerebellar ataxia; SCA14; protein kinase C; PRKCG

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Spinocerebellar ataxia type 14 (SCA14) is an autosomal dominant neurological disorder characterized by slowly progressive ataxia, dysarthria, and nystagmus. Additional signs and symptoms can include myoclonus, tremor, dystonia, depression, and cognitive impairment. There is a wide range of age at disease onset, spanning all age groups from childhood to adulthood. Most frequently, however, onset appears to be during adulthood. Magnetic resonance imaging (MRI) demonstrates pronounced cerebellar atrophy in patients.[1] The disease gene was assigned to the long arm of chromosome 19 (19q13.4)[2,3] and identified as *PRKCG*.[4] The *PRKCG* gene is composed of 18 exons and encodes protein kinase C gamma (PRKCG). SCA14 has been diagnosed molecularly in patients of Japanese and European extraction.[4–14] Here we report a previously not recognized mutation in exon 2 of *PRKCG* in patients of a German family.

PATIENTS AND METHODS

Clinical Characteristics

All affected members of the three-generation family suffer from mild gait ataxia, which is transmitted as an autosomal dominant trait (Fig. 1A). The index patient (II/2) is presently 45 years old and came to clinical attention at age 34 because of dystonia of the right arm. The main complaint was a writing cramp. He reported a nonprogressive mildly disturbed balance, gait ataxia, and dysarthria since childhood. Brain MRI scans at age 36 and 40 revealed pronounced nonprogressive cerebellar atrophy. At age 40, progression of dystonia in the right arm was observed. He presented with dysarthria, mildly ataxic and unsteady gait, nystagmus, mild dysphagia, and decreased tendon reflexes of the upper and lower extremities. There are no sensory deficiencies. Laboratory tests of blood and spinal fluid were normal. His father (I/2) and aunt (I/3) also suffer from mild gait ataxia and disturbed balance since age 50 and 45, respectively. The index patient's cousin (II/3) primarily presents with dysarthria and mild gait ataxia. Patient II/2 has 3 children, healthy twin daughters (presently 13 years old) and a 14-year-old son (III/1) who did not start walking before

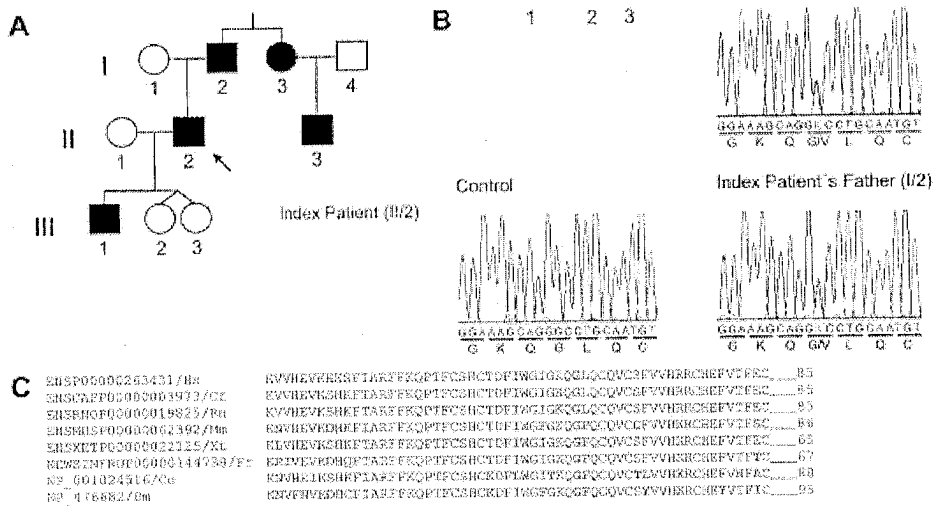

FIG. 1. **A:** Pedigree of the German spinocerebellar ataxia type 14 (SCA14) family. Black symbols indicate affected probands. The index patient is marked by an arrow. **B:** DNA sequence chromatograms of portions of *PRKCG* exon 2, showing the heterozygous G to T exchange in the index patient (II/2) and his father (I/2) compared to a control. Corresponding amino acid sequence is given. **C:** Amino acid sequence alignment of the Cys1 region of the C1 domain in PRKCG orthologs. Protein identifier numbers are given on the left. Amino acid residue numbers of PRKCG orthologs are indicated to the right of the sequences. The mutation at the highly conserved glycine residue is highlighted in red. Nonconserved residues are given in green. Hs, Homo sapiens; Cf, *Canis familiaris*; Rn, *Rattus norvegicus*; Mm, *Mus musculus*; Xl, *Xenopus tropicalis*; Fr, *Fugu rubripes*; Ce, *Caenorhabditis elegans*; Dm, *Drosophila melanogaster*. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

17 months of age and began to speak only at age 3.5 years. He now shows mildly disturbed balance and slight dysarthria. Myoclonus was not observed in any patient of the family.

Genetic Analysis

After exclusion of repeat expansions at loci SCA1, 2, 3, 6, 7, 12, 17, and DRPLA, we considered the diagnosis SCA14 based on the slow progression of ataxia in the index patient and autosomal dominant transmission in his family. We sequenced all 18 exons including exon–intron boundaries of *PRKCG* (Supplementary document) in the index patient and found a heterozygous G to T transversion at position 188 in exon 2 of the gene (Fig. 1B). The same mutation was detected in the patient's father but not in 200 healthy German controls (400 chromosomes). Other affected family members were not available for molecular testing. The G to T transversion results in the substitution of glycine by valine (G63V) in the cysteine-rich region 1/C1 domain of PRKCG (Fig. 1C).

DISCUSSION

PRKCG is a member of a serine/threonine kinase family that is involved in cellular processes such as cell proliferation and signal transduction.[15] PRKCG consists of an amino-terminal regulatory and a carboxyl-terminal catalytic domain. The regulatory portion of PRKCG is composed of the C1 and C2 domain. C1 contains two cysteine-rich regions (Cys1, Cys2). Cys1 and Cys2 interact with zinc ions and facilitate diacylglycerol/phorbolester binding. The C2 domain mediates calcium and phospholipid binding. The carboxyl-terminal catalytic C3/C4 domain is responsible for substrate recognition and phosphorylation.[15]

Several findings are consistent with the G63V change in PRKCG being the causative mutation in the family. First, it is only found in patients but not in controls. Second, it is located in an evolutionarily highly conserved domain of PRKCG (Cys1; Fig. 1C). Third, computer-based analysis using the SIFT algorithm (http://blocks.fhcrc.org/sift/SIFT.html) predicts that the G63V exchange is not tolerated in the Cys1 region.

The G63V mutation is the first one detected in exon 2 of *PRKCG* in a SCA14 patient. Previously described mutations are clustered in exon 4, and a few were found in exons 5, 10, 18, and 1 (summarized in Table 1). The only amino acid change detected in the Cys1 region before (R41P) is encoded by exon 1.[8] The phenotype of the family with the R41P mutation differed from that of the present individuals by absence of abnormal eye movements and absence of additional signs such as dystonia and decreased tendon reflexes, which were observed in the index patient of the present family. Of interest, two additional mutations in PRKCG, G118D[6]

TABLE 1. *Location of SCA14 mutations in the PRKCG gene*

Exon	Mutation	Domain	Reference
1 (aa 1-57)	R41P	Cys1, C1	8
2 (aa 58-67)	G63V	Cys1, C1	this paper
4 (aa 96-132)	H101Y	Cys2, C1	4
4 (aa 96-132)	H101Q	Cys2, C1	9
4 (aa 96-132)	del100K-101H	Cys2, C1	8
4 (aa 96-132)	C114Y	Cys2, C1	11
4 (aa 96-132)	G118D	Cys2, C1	6
4 (aa 96-132)	S119P	Cys2, C1	4
4 (aa 96-132)	S119F	Cys2, C1	13
4 (aa 96-132)	G123R; G123E	Cys2, C1	11
4 (aa 96-132)	Q127R	Cys2, C1	5
4 (aa 96-132)	G128D	Cys2, C1	4
4 (aa 96-132)	C131R	Cys2, C1	14
5 (aa 133-176)	V138E	Cys2, C1	12
5 (aa 133-176)	C150F	Cys2, C1	10
10 (aa 314-364)	G360S	C3/C4	11
10 (aa 314-364)	S361G	C3/C4	8
18 (aa 636-697)	F643L	C3/C4	7
18 (aa 636-697)	V692G	Variable region 5	11

aa, amino acid; Cys1, cysteine-rich region 1; Cys2, cysteine-rich region 2.

and V138E,[12] are associated with dystonia as well. These mutations are encoded by exons 4 and 5, respectively, and affect the Cys2 region of the C1 domain. Other exon 4 and 5 encoded mutations are not associated with dystonia.[1,13] These discrepant observations indicate that no straightforward genotype–phenotype correlation exists in SCA14.

We can only speculate about the physiological consequences of the G63V exchange. Alignment of the Cys1 and the Cys2 region of PRKCG shows that the glycine 63 residue in the Cys1 region corresponds to glycine 128 in the Cys2 region. By computer modeling, changes at position 128 were predicted to alter indirectly the shape of the phorbol ester binding site.[4] Therefore, the G63V exchange in the Cys1 region might affect phorbol ester binding as well.

A previous report specifically addressed the occurrence of *PRKCG* mutations in French and German SCA families. The authors, who focused on regions of *PRKCG* (exons 1, 3, 4, 5, 10, 18) in which mutations or polymorphisms had been detected previously, found mutations in French but not in German patients.[11] Very recently, the first SCA14 mutation in the German population was identified in exon 4 of *PRKCG* in a single family.[14] Our data stress the necessity to include all exons of *PRKCG* in the analysis of ataxia patients. The diagnosis SCA14 should even be considered in patients with very mild ataxia, slow progression of signs and symptoms, and other prominent features like focal dystonia.

Acknowledgments: The authors gratefully acknowledge the cooperation of the family members. We thank Christel Nohl for excellent technical assistance.

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